ReadyToProcess WAVE™ 25

The single-use ReadyToProcess WAVE 25 bioreactor system is a reliable and intuitive cell culture device for working volumes up to 25 L (Fig 1). The system is based on a well-known rocking technology that provides mixing and aeration to the culture, which is maintained in an inflated, disposable Cellbag™ bioreactor cultivation chamber. With ReadyToProcess WAVE 25, the rocking technology is enhanced with features such as advanced sensors and intelligent control strategies. System operation is easily managed via the intuitive and user friendly UNICORN™ system control software. The system is designed for fast installation and convenient handling, and delivers a reliable and accurate performance suitable for research, process development, and manufacturing operations.

Fig 1. ReadyToProcess WAVE 25 bioreactor system.

ReadyToProcess WAVE 25 offers the following benefits:

- Robust and reliable performance
- Intelligent and accurate process control
- Designed for ease of use
- Suitable for manufacturing in a regulated environment

System benefits

Robust and reliable performance

ReadyToProcess WAVE 25 is designed to make hardware, consumables, and software work together in an integrated manner. The system has been tested in real applications for reliable performance. To decrease the risk for data losses, the system comprises dual, mirrored, solid-state drives for data storage.

Intelligent and accurate process control

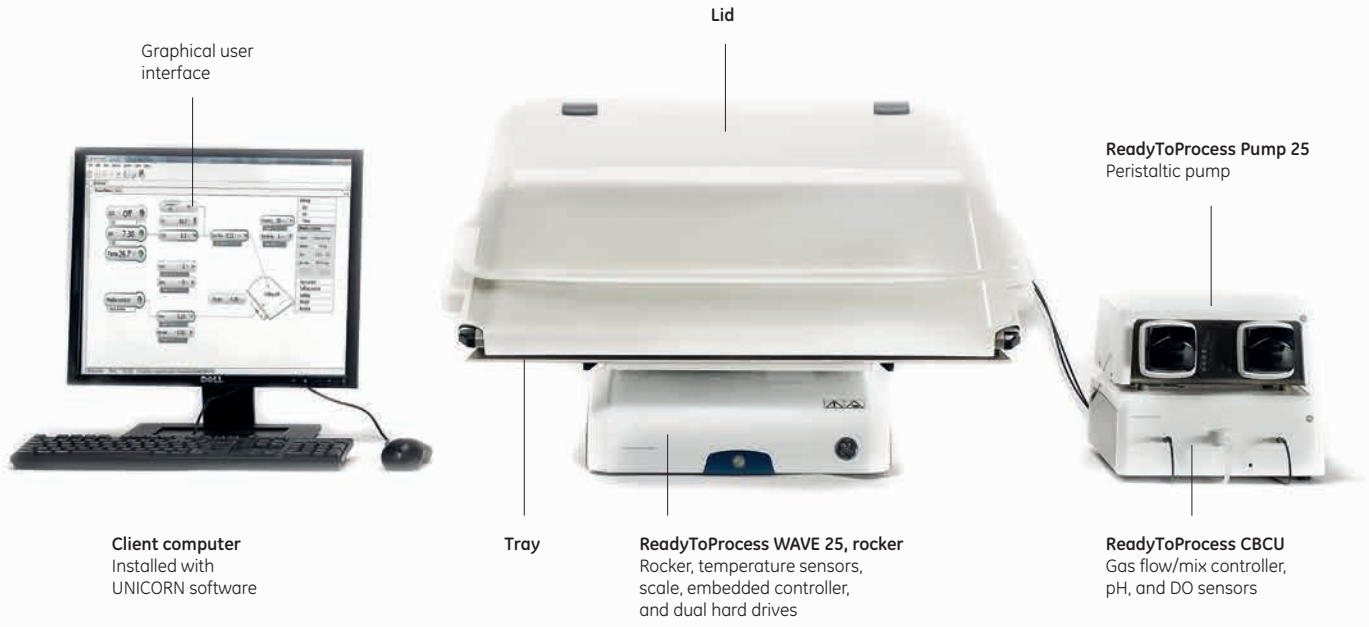
The system is equipped with advanced sensors and automated controllers for temperature, liquid handling, pH, and dissolved oxygen (DO). The system dynamics have been methodically characterized and the results used to create a library of predefined control parameters tailored for different cultivation volumes. The system can automatically determine suitable parameters for a run, a feature that facilitates fast start-up and enables accurate and stable control.

Easy to use

ReadyToProcess WAVE 25 system is designed for ease of use. Cellbag bioreactor attachment is straightforward and system operation is conveniently managed with the UNICORN software, with menus and process pictures that are easily accessible and interpretable. The harvest operation is facilitated by an innovative tilt function that omits the need for heavy lifting.

Suitable for manufacturing in a regulated environment

ReadyToProcess WAVE 25 is designed to meet the demands and standards that are required in a regulated environment. The documentation is extensive and includes material certificates, system specifications, installation and operational qualification (IQ/OQ) protocols, and a detailed user manual. The UNICORN software is suitable for use in a manner that complies with 21 CFR Part 11 and Good Automated Manufacturing Practice (GAMP) 5.



System setup and integration of subunits

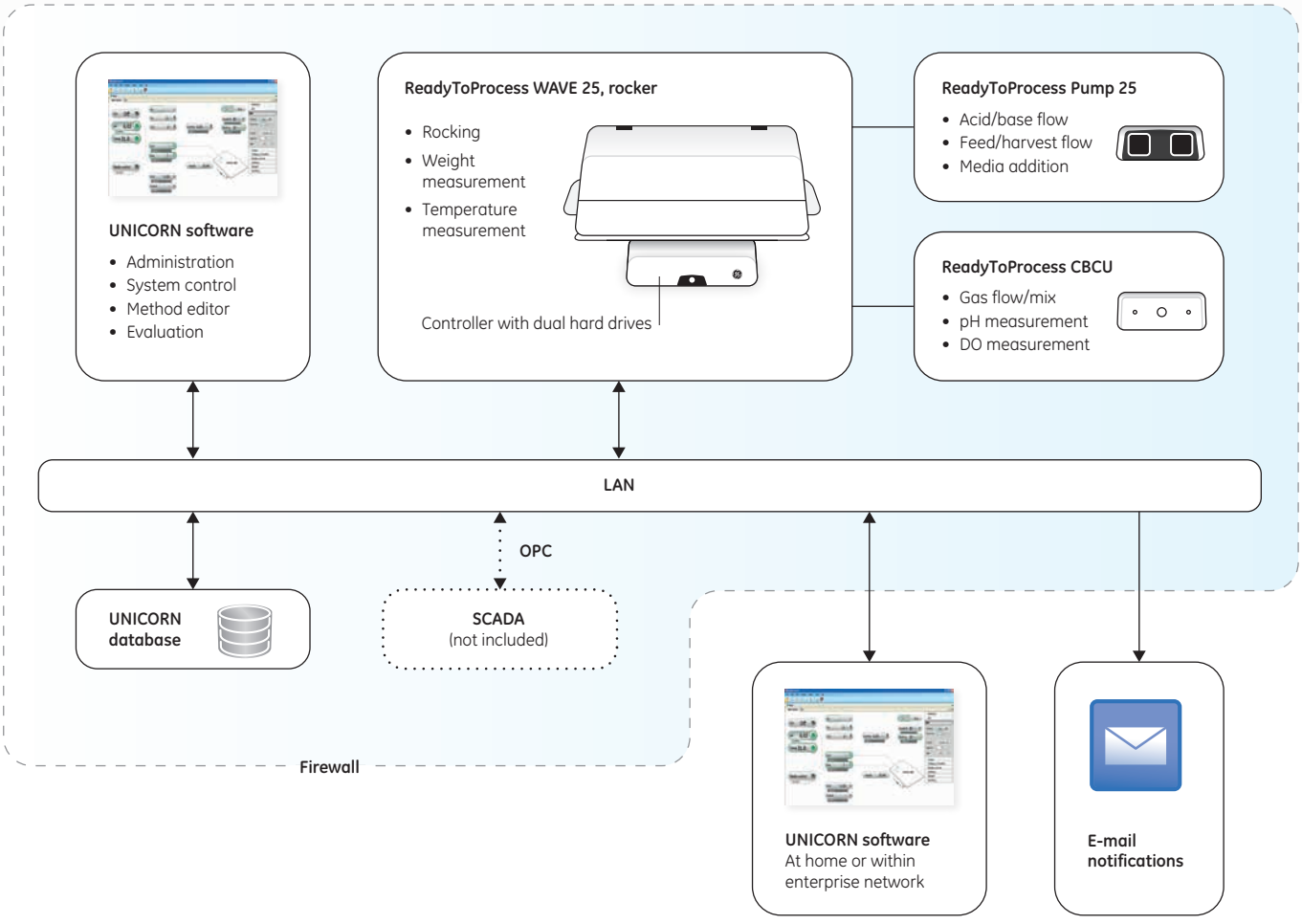


Fig 2. ReadyToProcess WAVE 25 system overview. The System Control module on the client computer is used to start and monitor the cultivation process. One UNICORN client can control up to three ReadyToProcess WAVE 25 systems simultaneously. SCADA = supervisory control and data acquisition, OPC = open platform communications, LAN = local area network.

System overview

ReadyToProcess WAVE 25 system components

The ReadyToProcess WAVE 25 system consists of a rocker, a gas mixer, and a pump, all operated by the UNICORN software installed on a client computer. The rocker is the main unit and is used together with a tray and a disposable Cellbag bioreactor. The rocker has multiple functions, amongst them heating, culture mixing, and weight measurement. The gas mixer delivers gas of a defined composition to the culture and is used, together with the optical sensors of the Cellbag bioreactor, for online control of culture pH and DO. Liquid is delivered accurately to the culture by ReadyToProcess Pump 25. The pump unit has a flow range covering multiple applications, from additions of feed and base to perfusion culturing. An overview of the ReadyToProcess WAVE 25 system is shown in Figure 2. The individual components are described in detail below.

ReadyToProcess WAVE 25, rocker

The rocker is the main hardware unit of the system and provides mixing through the rocking, reliable temperature measurement from integrated sensors, and accurate weight measurement from integrated load cells. The ergonomic design makes handling convenient and easy. The ability to handle the bioreactor in a tilt position facilitates sampling and harvest (Fig 3). The minimal footprint facilitates placement when space is limited.

A)

B)

Fig 3. (A) ReadyToProcess WAVE 25 in tilt position. (B) The ergonomic design makes activities such as sampling and harvest convenient and easy.

Trays and lids

Trays are available in three different sizes for culturing of up to 5 L, 10 L, and 25 L. The trays are easily attached to the rocker when in the tilt position. A snap lock mechanism allows Cellbag bioreactors to be correctly installed and rapidly changed (Fig 4). To protect light-sensitive components of the culture medium and to prolong the life of the optical sensors, lids are available for all tray sizes.

Fig 4. The tray has an easy lock mechanism for convenient and proper attachment of Cellbag bioreactors.

Temperature control

Reliable, efficient, and evenly distributed heating is provided by the tray heater plate. The temperature measurement is managed by sensors integrated in the rocker base unit (Fig 5). To minimize the risk for overheating, heating is only enabled when the rocker is in motion. For an accurate, stable, and fast temperature control, the heater power output is automatically adjusted based on the Cellbag bioreactor size and the media volume.

Fig 5. Integrated temperature sensors for convenient handling and reliable temperature control.

Mixing and gas transfer

The adjustable rocking parameters are speed, angle, and motion. The parameter settings, in combination with the cell culture volume, affect the mixing and gas transfer rate in the Cellbag bioreactor. The speed parameter determines the number of rocking cycles per minute, and the angle parameter relates to the tray's degree of tilting at the turning points. The motion parameter determines the acceleration profile. The lowest motion parameter setting, 15%, gives

an almost constant speed throughout the rocking cycle, whereas the highest setting, 100%, gives a faster speed in the middle of the cycle and slower at the turning points (Fig 6). A lower percent setting will give a more aggressive mixing with higher gas transfer rates. A higher setting will result in a smoother wave suitable for more delicate applications, such as adherent cultivation on microcarriers.

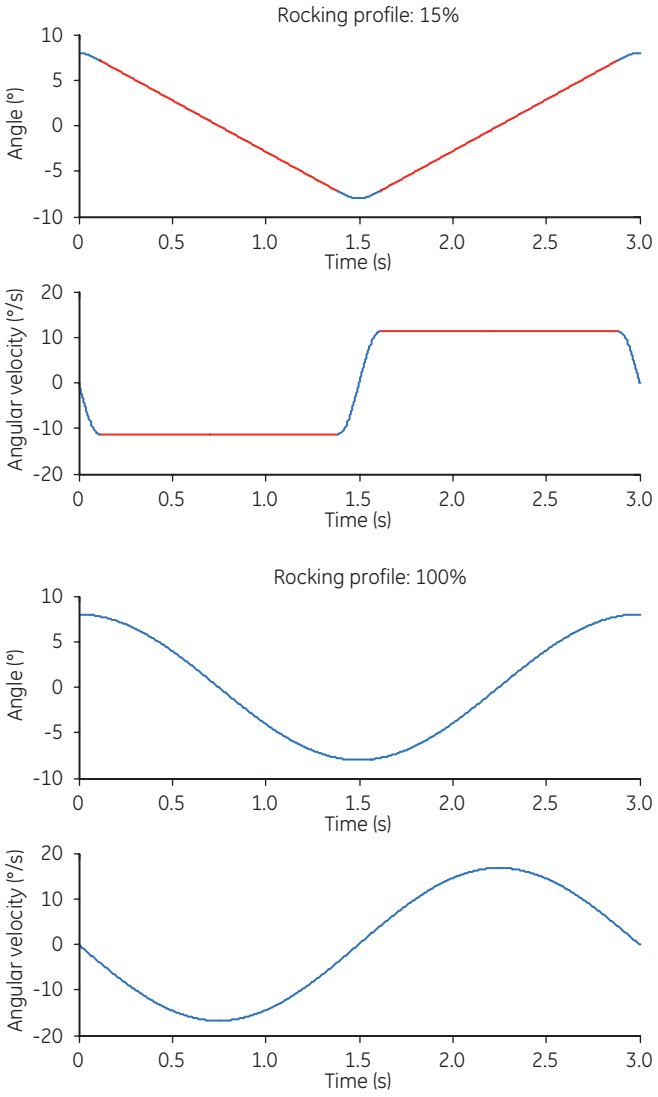


Fig 6. A user-defined rocking motion can be selected in UNICORN system control software. The wave can be aggressive or gentle, with subsequent impact on mixing and gas transfer in the culture.

Weight measurement

Load cells integrated in the rocker provide accurate and continuous weight measurement of the culture and eliminate the need for external scales. The load cells communicate with the system control function for proper media handling and for tailored regulation of pH and temperature. The weight measurement functionality is also used for automatic calibration of the pump in perfusion cultures. Adjustable feet enables equal weight distribution between the load cells also on nonlevel surfaces, for increased precision of the weight measurement.

Data storage and communication

All run data and control parameters are stored on two independent, mirrored, solid-state drives integrated in the rocker. Thus, once cultivation has been started and data from the instrument modules have been collected, the run can continue without the need for a network connection. The use of two solid-state drives enables culturing without losing any data even if only one drive is functional. After a run, data is stored in a UNICORN database on an external computer. For facilitated integration into a larger manufacturing operation, the rocker also contains software for enabling direct communication with the system via an open platform communication (OPC) link.

ReadyToProcess CBCU

The ReadyToProcess CBCU gas mixer is a compact unit with multiple functions. The unit is primarily used for providing gas to the culture and for monitoring of pH and DO. The unit contains a controller for mass flow, sensors for gas pressure and O_2 and CO_2 concentrations, and transmitters for pH and DO (Table 1).

Three CBCU configurations are available:

- CO_2, O_2, and pH
- CO_2, O_2, and DO
- CO_2, O_2, pH, and DO

The most suitable CBCU configuration will depend on the specific application.

Table 1. ReadyToProcess CBCU gas mixer overview

Feature	Description
CO_2/O_2/air mix controller	Depending on the configuration, air is mixed with CO_2 and/or O_2 according to the set-points. Nitrogen may be used instead of air for maintaining a low oxygen environment for near-anaerobic applications.
Gas flow controller	The gas-mix flow is measured and controlled by a mass flow controller (MFC). A correct volumetric flow is achieved by compensation for CO_2 concentration. Quick filling of gas into the Cellbag bioreactor, enabled by the fast-fill function, significantly reduces start-up time. An alarm will inform the user if pressure sensors detect under- or overpressure at the gas inlets or within the Cellbag bioreactor.
pH measurement	The pH is measured with optical pH sensors preinstalled in Cellbag bioreactors of pHOPT type. The sensor is connected to the CBCU via an optical fiber cable.
DO measurement	The DO level is measured with optical DO sensors preinstalled in Cellbag bioreactors of DOOPT type. The sensor is connected to the CBCU via an optical fiber cable.

ReadyToProcess Pump 25

The ReadyToProcess Pump 25 is a peristaltic unit incorporating two roller pumps for feed, harvest, and pH control. The pump design makes tubing installation convenient and easy. Tubing sizes from 0.5 mm (1/50") to 4.8 mm (3/16") internal diameter can be used to support flow rates from 0.07 to 100 mL/min. Flow rate is regulated by weight feedback from the scale and is controlled by automatic adjustments of the pump speed. Manual adjustment of the flow rate is also possible.

Media handling and perfusion using calibrated pumps

Calibration of pumps can be performed manually or automatically during an ongoing perfusion process. Automatic calibration is possible for flow rates above 3.5 L/d and is easily managed by entering the tubing diameter.

Automated pH control

To minimize fluctuations in pH during adjustments with CO_2/base or acid/base, the flow rate of the acid/base pumps needs to be rigorously monitored. The ReadyToProcess WAVE 25 system uses combined information from the load cells, the current process pH value, the pump tubing diameter, and the acid/base molarity for calculation of the needed flow rate during the run.

UNICORN software

UNICORN system control software consists of four modules: ***Administration, Method Editor, System Control***, and ***Evaluation***. A comprehensive help tool is also included.

Administration

The ***Administration*** module is used to administer all functions of the UNICORN software. Available functions include user and email setup, controlling access to groups and network users, defining and editing system properties, database management, and logging records of usage and activity.

Method editor

Instructions to control a bioreactor run can be defined in a method. The ***Method Editor*** module is used to create, edit, save, and work with methods. An existing method can be changed to simplify the editing process. Individual changes can be saved for later use on systems having the same instrument and component configuration.

System control

The ***System Control*** module is used to connect to the system as well as to start, view, and control a run (Fig 7). Default parameter values for an instrument can be viewed and edited in the ***System Settings*** dialog before a run is started or during an ongoing run using manual instructions. It is also possible to connect to other systems.

The user-friendly and intuitive ***Process Picture*** pane enables manual interaction with the system and provides status of the run parameters. Data is shown in the process picture but can also be viewed as curves in the ***Charts*** tab and as numerical values in the ***Run Data*** pane. Curves and information about the run are saved in a database, which can be opened in the ***Evaluation*** module. The default view shows the most commonly curves used. The user may customize which curves to display and the color and style of the displayed curves.

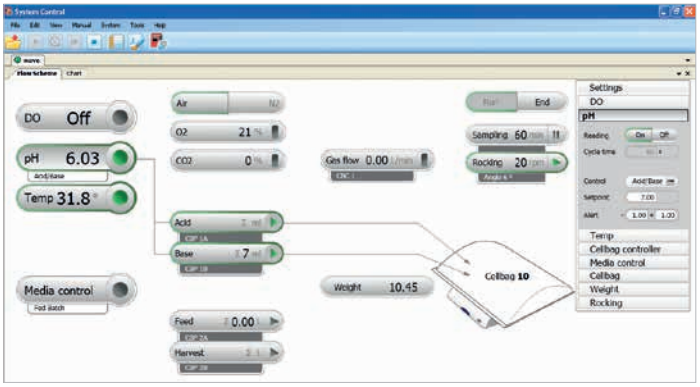


Fig 7. Monitoring and controlling all aspects of the culture is managed through the user-friendly interface.

Evaluation

In the ***Evaluation*** module, content of the result files can be viewed, analyzed, and compiled as reports. Reports can be customized, saved, and printed.

Automation of process parameters in pH and DO control

The UNICORN software automatically sets the desired PID* control parameters based on Cellbag bioreactor size and gas flow set-point. The system also adapts the parameters during the run, for optimization to reach a new set-point or to maintain a current set-point.

* Proportional-integral-derivative

Alarms, notifications, and data logging

The UNICORN software allows easy access to all operations, data, and alarm conditions. A dynamic, graphical user interface shows the real-time status of the run, while data are automatically saved. From the UNICORN software, the system is easily configured to trigger an alarm when certain conditions are met. Individual deviation alarms can be set for all essential parameters (heating, gas flow, CO_2, pH, and DO). The regulation of alarm sensitivity and delay is defined by the user. If such an alarm condition is triggered, the part of the system generating the alarm is highlighted in the graphical user interface and an alarm dialog is displayed. The alarm dialog displays information about the alarm, such as date and time of occurrence, as well as a help text describing the cause of the alarm and how to solve the problem. The system is easily configured to send email notifications of alarms and errors.

Regulatory readiness

The ReadyToProcess WAVE 25 system is suitable for biomanufacturing of regulated products under various Quality Management Systems. The use of UNICORN software in a 21 CFR Part 11 and GAMP 5 compliant manner enables use of the system in a regulated environment. Individual user access permissions can be set and individual users are password-protected. Active processes can be locked to enable unattended operations without the risk of unauthorized interference. All records are stored in a single, unalterable database, including results and extended run documentation. Additional validation support includes comprehensive documentation on control system validation as well as IQ/OQ services. Available validation support documentation includes:

- Detailed description of the development model used for UNICORN software
- 21 CFR Part 11 system assessment in checklist format
- Audit report and 21 CFR Part 11 conclusion on functionality by an external, independent expert

Networking capabilities

UNICORN software operates in Windows XP® and Windows® 7 environments and the network ability allows real-time control from a remote or local computer. Communication is Ethernet-based and each instrument is controlled by a dedicated instrument server. One database can be connected to 32 systems and up to three instruments can be controlled simultaneously from one UNICORN client.Results are saved locally, in the rocker, during the run and then stored on the database server. Because results and instructions are saved locally on the embedded drives, a run can continue even in the event of a network communication failure.

UNICORN software can be integrated in a supervisory control and data acquisition (SCADA) system such as the Emerson DeltaV™ control system using the UNICORN OPC server.

Cellbag bioreactors

Cellbag bioreactors are single-use bags for the noninvasive mixing of culture medium and cells during cultivation (Fig 8). Cellbag bioreactors require no sterilization or cleaning steps. The disposable bioreactors provide a suitable environment for cell growth while minimizing the cross-contamination risk. The bags are manufactured from multilayer, laminated, clear USP Class VI plastics and are easily connected to the full suite of ReadyToProcess cell culture, purification, and fluid handling products. The selection of Cellbag bioreactors is listed in Table 2. For more information about Cellbag bioreactors, see data file 28-9511-36.

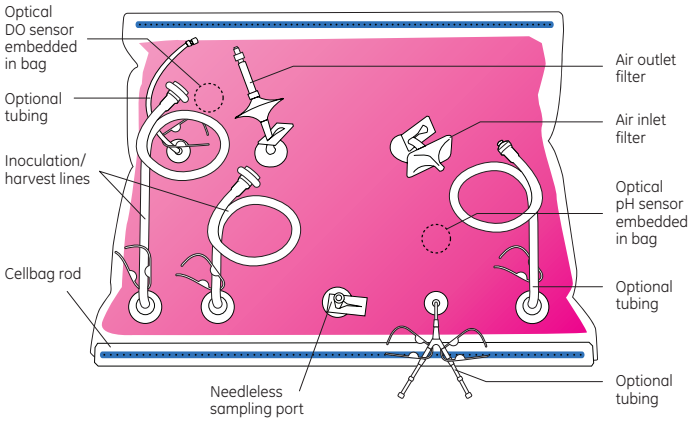


Fig 8. Presentation of typical Cellbag bioreactor fittings.

Table 2. Selection of Cellbag bioreactor sizes

Cellbag bioreactor*	Working volume
Cellbag 2 L	300† mL to 1 L
Cellbag 10 L	500 mL to 5 L
Cellbag 20 L	1 to 10 L
Cellbag 22 L	1 to 10 L
Cellbag 50 L	5 to 25 L

* All Cellbag bioreactor sizes are available with internal perfusion filter for perfusion cultures and/or can be equipped with single use optical pH (pHOPT) and DO (DOOPT II) sensors.

† Cellbag bioreactors with optical sensors require 300 mL minimal working volume. Depending on application and configuration, it might be possible to cultivate below the recommended minimum volume. However, it is highly recommended to stay above this volume for applications that require high agitation and pH and DO control. The temperature, pH, and DO sensors need to be submerged in liquid throughout the complete rocking cycle to function correctly.

System specifications

System specifications are listed in Table 3.

Table 3. ReadyToProcess WAVE 25 system specifications

General system specifications

Control system	UNICORN 6.3.2 or later version	
Dimensions, W × H × D		
Rocker	404 × 205 × 560 mm	
Tray 10	475 × 60 × 430 mm	
Tray 20	740 × 70 × 480 mm	
Tray 50	800 × 70 × 610 mm	
Lid 10	475 × 230 × 430 mm	
Lid 20	740 × 245 × 480 mm	
Lid 50	800 × 260 × 610 mm	
CBCU	276 × 117 × 360 mm	
Pump 25	275 × 115 × 280 mm	
Weight		
Rocker	24.0 kg	
Tray 10	4.5 kg	
Tray 20	7.3 kg	
Tray 50	9.5 kg	
Lid 10	1.7 kg	
Lid 20	3.3 kg	
Lid 50	3.9 kg	
CBCU	4.8 kg	
Pump 25	3.8 kg	
Power supply	100 to 240 V, ~ 50 to 60 Hz	
Power consumption	1500 VA	
Enclosure protective class	IP 21	
Gas supply	Normal capacity	Fast-fill capacity
External air supply, 1.0 to 1.5 bar	1.3 L/min	3.5 L/min
External CO_2 supply, 1.0 to 1.5 bar	0.2 L/min	0.5 L/min
External O_2 supply, 1.0 to 1.5 bar	0.7 L/min	1.7 L/min

Environmental aspects

Operating ambient temperature range	15°C to 32°C
Operating humidity range	20% to 80% relative humidity (noncondensing)

ReadyToProcess WAVE 25, rocker

Rocking speed control range[1]	2 to 40 rpm
Rocking angle control range[1]	2° to 12°
Rocking motion control range	15% to 100%
Media weight control range	0.5 to 25 kg
Scale, absolute accuracy	± (0.050 + 1% of load) kg
Temperature sensor	Pt100 Class A
Temperature measurement range	2°C to 50°C
Temperature control range	(ambient temperature + 5°C) to 40°C
Temperature control accuracy (excl. measurement error)	± 0.2°C

[1] When cultivating in a 50 L Cellbag bioreactor at maximum working volume of 25 L, rocking speed and angle multiplied should not exceed 240 rpm degrees. For example, if the rocking angle is set to 12 degrees, the rocking speed should not be set higher than 20 rpm.

ReadyToProcess CBCU

Gas flow control range	50 to 1000 mL/min
Total gas flow accuracy (reference flow - setpoint)	± (10 + 3% of read value) mL/min
Fast-fill flow	~ 3 L/min
CO_2 control range	0% to 15% CO_2
CO_2 measurement accuracy at 5% CO_2	± 0.5% CO_2 when mixed only with air/N_2
CO_2 control accuracy (versus setpoint)	± 0.4% CO_2
O_2 control range	0% to 50% O_2 when mixed with N_2, 21% to 50% O_2 when mixed with air
O_2 measurement accuracy	± (0.6% + 1% of read value) % O_2 within 0% to 50% O_2 when mixed only with air/N_2
O_2 control accuracy (versus setpoint)	± 0.6% O_2
pH measurement range	pH 4.5 to 8.5
pH control range	pH 6.0 to 8.0
pH measurement accuracy	± 0.05 pH within ± 0.25 pH from offset calibration pH ± 0.1 pH within 0.25 to 0.5 pH from offset calibration
pH control accuracy (versus setpoint)	± 0.05 pH
DO measurement range	0% to 250% air saturation
DO measurement accuracy	± 5% air saturation (excl. atmospheric pressure variations)
DO control range	0% to 100% air saturation

ReadyToProcess Pump 25

Pump flow rate range	0.1 to 144 L/d (0.07 to 100 mL/min)
Pump flow accuracy	± (0.1 + 5% of read value) mL/min after calibration
Accumulated pumped volume accuracy	± 10% of measured volume
Supported tubing dimensions	i.d. 0.5 to 4.8 mm (1/50" to 3/16") wall thickness: 1.6 mm (1/16")

Applications

ReadyToProcess WAVE 25 is designed for a variety of cell culture applications involving mammalian, insect, and plant cells:

- Batch culture
- Fed-batch culture
- Perfusion culture
- Cultivation of adherent cells

Ordering information

Product	Description	Code number
ReadyToProcess WAVE 25	Rocker	28-9880-00
ReadyToProcess CBCU pH	Gas flow/mix and pH	29-0442-13
ReadyToProcess CBCU DO	Gas flow/mix and DO	29-0442-16
ReadyToProcess CBCU Full	Gas flow/mix, pH, and DO	29-0440-81
ReadyToProcess Pump 25	Pump	29-0320-03
UNICORN 6.3.2 WrkStn-pure-BP	Software and license	29-0469-18
UNICORN 6.3 Remote License	–	29-0203-51
UNICORN 6.3 Dry license	–	29-0203-55
Tray 10	–	29-0444-72
Tray 20	–	29-0444-73
Tray 50	–	29-0444-74
Lid 10	–	29-0444-75
Lid 20	–	29-0444-76
Lid 50	–	29-0444-77
Filter heater	–	29-0444-71
Bag sensor adaptor 2.5 m assembly	Fiber cable for pH and DO control	28-9841-89

Related literature	Code number
UNICORN 6.3 Manual Package	29-0234-67
UNICORN 6 control software, data file	28-9573-46
Disposable Cellbag bioreactors for WAVE Bioreactor systems, data file	28-9511-36
Validation Support File UNICORN 6.3	11-0029-94

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